IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

SMITH KLINE & FRENCH LABORATORIES LIMITED and SMITHKLINE BEECHAM CORPORATION d/b/a GLAXOSMITHKLINE, Plaintiff, v. TEVA PHARMACEUTICALS USA, INC., Defendant.	Civil Action No. 05-197-GMS **PUBLIC VERSION**

DECLARATION OF MARK L. RIENZI IN SUPPORT OF PLAINTIFF GLAXOSMITHKLINE'S OPPOSITION TO DEFENDANT'S MOTION *IN LIMINE* NO. 1 TO EXCLUDE EVIDENCE AND TESTIMONY ON COMMERCIAL SUCCESS

I, Mark L. Rienzi, declare as follows:

I am admitted to this Court, and I am an attorney with the law firm of Wilmer Cutler Pickering Hale and Dorr LLP, counsel of record for the Plaintiff GlaxoSmithKline in this action.

1. Attached hereto as Exhibit A is a true and correct copy of excerpts from the Deposition of Kevin H. Reeves.

2. Attached hereto as Exhibit B is a true and correct copy GSK-REQ 094245-094254.

3. Attached hereto as Exhibit C is a true and correct copy of GSK-REQ136060-136069.

4. Attached hereto as Exhibit D is a true and correct copy of the Expert Report of Christopher A. Vellturo.

5. Attached hereto as Exhibit E is a true and correct copy of excerpts from the rough transcript of the Deposition of Daniel Tarsy, M.D.

6. Attached hereto as Exhibit F is a true and correct copy of "A Five-Year Study of the Incidence of Dyskinesia in Patients with Early Parkinson's Disease who were Treated with

Ropinirole or Levodopa," N. Eng. J. Med. 2000 (342) 1484-1491, produced at GSK-REQ092497-092505.

7. Attached hereto as Exhibit G is a true and correct copy of Miyasaki, J.M., *et al.*, "Practice parameter: Initiation of treatment for Parkinson's disease: An evidence-based review: Report of the Quality Standards Subcommittee of the American Academy of Neurology", *Neurology* (58) January 2002, 11-17, produced at GSK-VEL000126-000134.

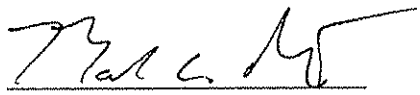
8. Attached hereto as Exhibit H is a true and correct copy of the Corrected Expert Report of Harry C. Boghigian.

9. Attached hereto as Exhibit I is a true and correct copy of excerpts from the Deposition of Ann Payne.

10. Attached hereto as Exhibit J is a true and correct copy of Defendant Teva Pharmaceuticals U.S.A., Inc.'s Responses to Plaintiffs' First Set of Requests for Production of Documents and Tangible Things.

I declare under penalty of perjury that the foregoing is true and correct. Executed in Washington, D.C.

Respectfully submitted,



Mark L. Rienzi

Dated: October 30, 2006

Exhibit A

(exhibit has been redacted in its entirety)

Exhibit B

(exhibit has been redacted in its entirety)

Exhibit C

(exhibit has been redacted in its entirety)

Exhibit D

(exhibit has been redacted in its entirety)

Exhibit E

(exhibit has been redacted in its entirety)

Exhibit F

Reprinted From

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A FIVE-YEAR STUDY OF THE INCIDENCE OF DYSKINESIA IN PATIENTS WITH EARLY PARKINSON'S DISEASE WHO WERE TREATED WITH ROPINIROLE OR LEVODOPA

OLIVIER RASCOL, M.D., PH.D., DAVID J. BROOKS, M.D., D.SC., AMOS D. KORCZYN, M.D., PETER P. DE DEYN, M.D., PH.D., CARL E. CLARKE, M.D., AND ANTHONY E. LANG, M.D., FOR THE 056 STUDY GROUP*

ABSTRACT

Background There is debate about whether the initial treatment for patients with Parkinson's disease should be levodopa or a dopamine agonist.

Methods In this prospective, randomized, double-blind study, we compared the safety and efficacy of the dopamine D2-receptor agonist ropinirole with that of levodopa over a period of five years in 268 patients with early Parkinson's disease. If symptoms were not adequately controlled by the assigned study medication, patients could receive supplementary levodopa, administered in an open-label fashion. The primary outcome measure was the occurrence of dyskinesia.

Results Eighty-five of the 179 patients in the ropinirole group (47 percent) and 45 of the 89 patients in the levodopa group (51 percent) completed all five years of the study. In the ropinirole group, 29 of the 85 patients (34 percent) received no levodopa supplementation. The analysis of the time to dyskinesia showed a significant difference in favor of ropinirole (hazard ratio for remaining free of dyskinesia, 2.82; 95 percent confidence interval, 1.78 to 4.44; $P<0.001$). At five years, the cumulative incidence of dyskinesia (excluding the three patients who had dyskinesia at base line), regardless of levodopa supplementation, was 20 percent (36 of 177 patients) in the ropinirole group and 45 percent (40 of 88 patients) in the levodopa group. There was no significant difference between the two groups in the mean change in scores for activities of daily living among those who completed the study. Adverse events led to the early withdrawal from the study of 48 of 179 patients in the ropinirole group (27 percent) and 29 of 89 patients in the levodopa group (33 percent). The mean (±SD) daily doses given by the end of the study were 16.5±6.6 mg of ropinirole (plus 427±221 mg of levodopa in patients who received supplementation) and 753±398 mg of levodopa (including supplements).

Conclusions Early Parkinson's disease can be managed successfully for up to five years with a reduced risk of dyskinesia by initiating treatment with ropinirole alone and supplementing it with levodopa if necessary. (N Engl J Med 2000;342:1484-91.)

ALTHOUGH the antiparkinsonian effect of the dopamine precursor levodopa was first demonstrated 30 years ago,[1] and that of dopamine D2-receptor agonists more than 25 years ago,[2] the most appropriate time to begin these two treatments in patients with Parkinson's disease remains controversial.[3] Some neurologists promote the early use of levodopa, emphasizing the rapid symptomatic benefit[4] and the possible reduction in mortality that the drug provides.[5] Others, more concerned about the potential neurotoxicity[6] and the long-term complications, such as dyskinesia, associated with the use of levodopa,[7-11] encourage the early use of dopamine agonists. This long-standing controversy remains largely unresolved,[12] although recent data suggest that initiating treatment with a dopamine agonist confers some advantage.[13,14] Data from studies of monkeys treated with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine have demonstrated that dopamine agonists are less likely than levodopa to induce dyskinesia in animals that have not been exposed to levodopa.[15] Because dyskinesia is one of the most debilitating effects of levodopa therapy, we studied the incidence of dyskinesia associated with the two treatments in a large, prospective, randomized, five-year study.

Ropinirole is a non-ergot-derived D2-like dopamine-receptor agonist that is effective in the treatment of early[14,16,17] and late[18,19] Parkinson's disease. The effectiveness of ropinirole in the treatment of early Parkinson's disease has already been demonstrated through a planned interim analysis of the data from the study described here, conducted six months after the study was begun, in which the primary end point was the score for motor function on the Unified Parkinson's Disease Rating Scale (UPDRS).[17] We present here the results of the final five-year analysis, in which

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*The investigators who participated in the study are listed in the Appendix.

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the primary outcome measure was the incidence of dyskinesia.

METHODS

Study Population

A total of 268 patients were enrolled at 30 centers (in Europe, Israel, and Canada). All patients were 30 years of age or older, had a clinical diagnosis of Parkinson's disease[20] with a Hoehn–Yahr rating of stage 1 through 3 (with stage 1 indicating unilateral, early disease and stage 3 more advanced, bilateral disease),[21] and required dopaminergic therapy. Prior short-term treatment with levodopa or dopamine agonists was limited to a maximum of six weeks and had to be discontinued at least two weeks before entry into the study.

Patients were excluded if they had severe dizziness or fainting, severe systemic disease, major psychosis, severe dementia, alcoholism or drug dependence, or a contraindication to levodopa. In addition, treatment with a monoamine oxidase inhibitor within two weeks before entry (with the exception of selegiline) or previous treatment with ropinirole were reasons for exclusion.

Study Design

This prospective, randomized, double-blind study was designed to compare the risk of dyskinesia in early Parkinson's disease among patients treated with ropinirole (Requip, SmithKline Beecham, Philadelphia) with that among patients treated with a combination of levodopa and benserazide (Madopa, Hoffmann–LaRoche, Nutley, N.J.; referred to hereafter as levodopa) over a period of five years. Random treatment assignment was performed with a ropinirole-to-levodopa ratio of 2:1. Benserazide has been shown previously to have properties that are similar to those of carbidopa (used with levodopa in Sinemet [Dupont Merck, Wilmington, Del.]) in blocking dopa decarboxylase in the periphery.[22,23] Blinding of the study was maintained with the use of a double-dummy technique. Sealed copies of the randomization code were held by the principal investigator at each site and by the study sponsor.

Patients underwent a single-blind placebo run-in period lasting seven days to demonstrate at least 80 percent compliance with taking study medication. Patients were then randomized (with stratification according to whether they were receiving concomitant selegiline therapy), and assessments were performed at weekly intervals for the first month, every two weeks for the next two months, every month up to six months, and every two months thereafter.

The study was conducted in accordance with Good Clinical Practices guidelines and the Declaration of Helsinki. The protocol was approved by an ethics committee at each center, and written informed consent was obtained from each patient.

Treatment

Both ropinirole and levodopa were taken orally in tablet form. The dose of study medication was adjusted weekly as required, with 13 possible increasing dose levels. Ropinirole therapy was initiated (dose level 1) at 0.75 mg per day (0.25 mg three times daily) and levodopa therapy at 50 mg once daily plus placebo twice daily. The maximal daily doses of study medication allowed (dose level 13) were 24 mg of ropinirole per day (8 mg three times daily) and 1200 mg of levodopa per day (400 mg three times daily). Investigators were encouraged to treat patients only with the assigned study medication. Patients whose symptoms were not adequately controlled by the adjustment of study medication alone (i.e., those with recurrent, persistent, or functional disability), despite use of the highest tolerated dose, could be given supplementary levodopa in open-label fashion. No other antiparkinsonian therapies were permitted after the start of the study. Domperidone was permitted according to the normal practice at each individual study center, to control severe dizziness, nausea, or vomiting.

Clinical Assessments

Dyskinesia

Dyskinesia (the incidence of which was assessed in patients before withdrawal from the study or until completion of the study) was considered to be present if a patient had a score of 1 or more (on a scale from 0 to 4, where a score of 0 indicates no dyskinesia and a score of 4 indicates dyskinesia during most waking hours) on item 32 of the UPDRS[24] ("Duration: what proportion of the waking day are dyskinesias present?") or if dyskinesia was reported as an adverse event. In addition, all reports of adverse events consisting of abnormal movements considered to be dyskinesia were reviewed before the randomization code was broken.

Additional Variables

"Disabling" dyskinesia was defined as a score of 1 or more on items 32 and 33 of the UPDRS ("How disabling are the dyskinesias?").

The scores for activities of daily living and motor function were measured with the use of parts II and III of the UPDRS (items 5 through 17 [range of possible scores, 0 to 52, where 0 indicates no disability and 52 indicates maximal impairment] and items 18 through 31 [range of possible scores, 0 to 108, where 0 indicates no disability and 108 indicates maximal impairment]), respectively, for the patients who completed the study.

"Wearing off" (defined as periods of increased severity of parkinsonian symptoms as medication wears off) was assessed by reviewing the data from patients who reported increases in the duration of time awake and in an "off" period on item 39 of the UPDRS. "Freezing when walking" was assessed by reviewing responses to item 14 of the UPDRS.

Safety and Tolerability of the Drugs

Adverse events were assessed in a standard manner by the investigator. Neuropsychiatric adverse events (i.e., hallucinations, confusion, delirium, psychosis, illusion, delusion, depersonalization, personality disorder, abnormal thinking, amnesia, dementia, impaired concentration, and other related events, as defined by the World Health Organization) were the only predetermined measures of safety in the statistical analyses.

Statistical Analysis

We planned to enroll 240 patients into the study (160 randomly assigned to ropinirole and 80 to levodopa); this number was calculated on the assumption of an underlying rate of response to treatment of 85 percent. Samples of 110 patients in the ropinirole group and 55 in the levodopa group who could be evaluated at the six-month interim analysis[17] provided the study with an 80 percent chance of demonstrating equivalent efficacy in the two groups (with a 90 percent confidence interval), on the assumption that the response rate in the levodopa group would not be more than 15 percent higher than that in the ropinirole group. It was anticipated that 30 patients in the ropinirole group and 50 in the levodopa group would complete all five years (predicted withdrawal rates, 30 percent and 10 percent per year, respectively). These numbers of patients provided the study with 88 percent power to detect a difference ($P<0.05$) in the incidence of dyskinesia between the two groups, assuming an incidence of 5 percent in the ropinirole group and an incidence of 30 percent in the levodopa group.

All analyses (except those based on the scores for activities of daily living and motor function) were performed on an intention-to-treat basis and include all randomized patients who had at least one assessment after receiving study medication. Patients were not followed up for assessment of dyskinesia after withdrawal from the study.

The rates of dyskinesia and disabling dyskinesia in the two groups were compared with the use of the Cox proportional-hazards model[25] in an analysis of failure time (time to an episode of dyskinesia or disabling dyskinesia). Kaplan–Meier curves,[26] haz-

ard ratios with 95 percent confidence intervals, and P values were calculated. Data on patients were censored at the time they withdrew from the study without having dyskinesia.

Statistical analyses of variance of the mean changes in the scores for activities of daily living and motor function between base line and the end of the study were based on data from the patients who completed the study. The results of these analyses are presented as adjusted treatment differences, with 95 percent confidence intervals and P values. It was not possible to analyze these scores over the duration of the study without bias because the number of patients at each time point varied and because of the problems with performing multiple tests.

The proportions of patients with neuropsychiatric adverse events in the two groups were compared with the exact chi-square test.

Statistical tests were performed using two-tailed tests at the 5 percent level of significance.

RESULTS

Patients and Treatment

Of the 268 patients who entered the trial, 179 were randomly assigned to ropinirole and 89 to levodopa (Fig. 1). The demographic characteristics of the two groups were similar (Table 1). Two patients in the ropinirole group and one in the levodopa group had dyskinesia at base line and were excluded from the analyses of the incidence of dyskinesia. Eighty-five of the patients in the ropinirole group (47 percent) and 45 of those in the levodopa group (51 percent) completed the study. Of these patients, 29 in the ropinirole group (34 percent) and 29 in the levodopa group (64 percent) did so without open-label levodopa supplementation. The reasons for withdrawal from the study are presented in Figure 1.

Mean (±SD) daily doses at the completion of the study were 16.5±6.6 mg of ropinirole (plus 427±221 mg of open-label levodopa in patients requiring supplementation) and 753±398 mg of levodopa (including open-label supplements). Fifty-two patients in the ropinirole group (29 percent) and 24 in the levodopa group (27 percent) received domperidone at some time during the five-year study.

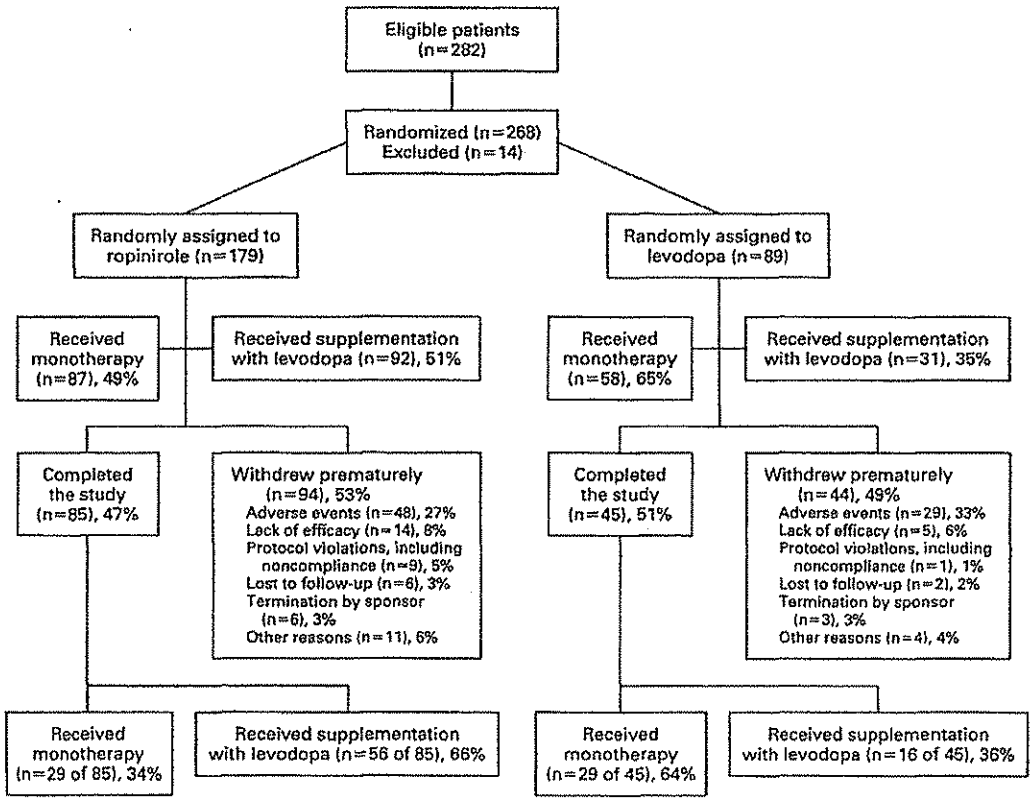


Figure 1. Enrollment and Treatment of the Study Patients.

"Termination by sponsor" refers to one center that was closed early by agreement with the investigator because of noncompliance with the protocol.

TABLE 1. CHARACTERISTICS OF THE INTENTION-TO-TREAT POPULATION.*

CHARACTERISTIC	ROPINIROLE (N=179)	LEVODOPA (N=89)
Age — yr	63±9	63±9
Sex — no. (%)		
Male	113 (63.1)	52 (58.4)
Female	66 (36.9)	37 (41.6)
Selegiline treatment at start of study — no. (%)	81 (45.3)	39 (43.8)
Prior levodopa treatment for ≤6 wk — no. (%)	26 (14.5)	7 (7.9)
Duration of disease — mo	30±34	29±27
Hoehn–Yahr stage — no. (%)†		
1	23 (12.8)	20 (22.5)
1.5	27 (15.1)	8 (9.0)
2	66 (36.9)	33 (37.1)
2.5	46 (25.7)	19 (21.3)
3	17 (9.5)	9 (10.1)
UPDRS Score‡		
Base-line score for ADL	8.0±5.0	8.0±4.6
Base-line for motor function score	21.5±10.5	21.7±11.3

*Plus–minus values are means ±SD.

†The stages range from 1, indicating unilateral, early disease, to 3, indicating more advanced, bilateral disease.

‡UPDRS denotes Unified Parkinson's Disease Rating Scale, and ADL activities of daily living. The range of possible scores for activities of daily living is 0 to 52, with a higher score indicating more severe dysfunction. The range of possible scores for motor function is 0 to 108, with a higher score indicating more severe dysfunction.

Incidence of Dyskinesia

The reduced risk of dyskinesia among the patients in the ropinirole group, regardless of levodopa supplementation, is evident in Figure 2 (hazard ratio for remaining free of dyskinesia in the ropinirole group, as compared with the levodopa group, 2.82; 95 percent confidence interval, 1.78 to 4.44; $P<0.001$). There were too few patients with dyskinesia in the ropinirole group to calculate the length of time until dyskinesia developed in 50 percent of the patients remaining in the study. However, the length of time until dyskinesia developed in 25 percent of the patients remaining in the study was 214 weeks among the patients in the ropinirole group and 104 weeks among the patients in the levodopa group. Overall, dyskinesia developed in 36 of the 177 patients in the ropinirole group (20 percent) and in 40 of the 88 in the levodopa group (45 percent), as assessed by item 32 of the UPDRS and by reports of adverse events. Before the addition of supplementary levodopa, 9 of 177 patients in the ropinirole group (5 percent) and 32 of 88 in the levodopa group (36 percent) had dyskinesia.

Other Variables

The risk of disabling dyskinesia was significantly lower in the ropinirole group, regardless of whether the patient received supplementary levodopa (hazard ratio for remaining free of disabling dyskinesia in the ropinirole group as compared with the levodopa group, 3.02; 95 percent confidence interval, 1.52 to 6.02; $P=0.002$). Fourteen of the 179 patients in the ropinirole group (8 percent) had disabling dyskinesia, as compared with 20 of the 89 in the levodopa group (23 percent).

Figure 3 shows the mean scores for activities of daily living throughout the study. Among the patients who completed the study, the mean (±SD) change from base line in the score for activities of daily living was an increase of 1.6±5.4 points (a slight worsening) among the patients in the ropinirole group and 0.0±4.7 points among those in the levodopa group. This difference was not significant (adjusted difference, 1.53 points; 95 percent confidence interval, −0.14 to 3.22; $P=0.08$).

Figure 3 also shows the mean scores for motor function during the study. For the patients who completed the study, there were mean decreases from base line in motor-function scores of 0.8±10.1 point (a slight improvement) among the patients in the ropinirole group and 4.8±8.3 points among those in the levodopa group. The difference in mean scores was significant in favor of levodopa (adjusted treatment difference, 4.48 points; 95 percent confidence interval, 1.25 to 7.72; $P=0.008$).

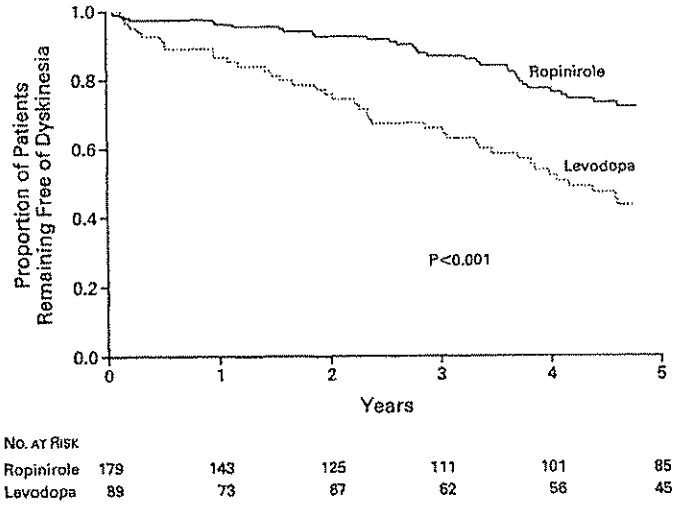
The length of time until 25 percent of the patients remaining in the study first had an increase in the wearing-off effect was 199 weeks in the ropinirole group and 145 weeks in the levodopa group. Of the patients for whom data were available, 39 of 172 patients in the ropinirole group (23 percent) and 29 of 85 in the levodopa group (34 percent) had an increase in symptoms due to the wearing off of the drugs during the study.

The length of time until 25 percent of the patients remaining in the study first had an increase in freezing while walking was 166 weeks in the ropinirole group and 207 weeks in the levodopa group. Of the patients for whom data were available, 57 of 178 patients in the ropinirole group (32 percent) and 22 of 88 in the levodopa group (25 percent) had an increase in freezing while walking.

Fourteen of the 179 patients in the ropinirole group (8 percent) withdrew from the study early because of a lack of efficacy, as compared with 5 of 89 in the levodopa group (6 percent). Aggravated parkinsonism was responsible for the withdrawal of 6 of the 179 patients in the ropinirole group (3 percent) and 3 of the 89 in the levodopa group (3 percent).

Adverse Events

Relevant adverse events that occurred in more than 10 percent of the study population over the course of the study are listed in Table 2. There was no significant difference in the incidence of neuropsychiat-



No. at Risk						
Ropinirole	179	143	125	111	101	85
Levodopa	89	73	67	62	56	45

Figure 2. Proportions of Patients Remaining Free of Dyskinesia in the Ropinirole and Levodopa Groups. The hazard ratio for remaining free of dyskinesia in the ropinirole group as compared with the levodopa group was 2.82 (95 percent confidence interval, 1.78 to 4.44).

ric adverse events between the two groups (43 of 179 patients in the ropinirole group [24 percent] and 15 of 89 patients in the levodopa group [17 percent]; P=0.18 by the chi-square test), although the incidence of hallucinations was higher in the ropinirole group (31 of 179 patients [17 percent]) than in the levodopa group (5 of 89 patients [6 percent]).

Adverse events caused the early withdrawal from the study of 48 of the 179 patients in the ropinirole group (27 percent) and 29 of the 89 patients in the levodopa group (33 percent). The two most common reasons for early withdrawal due to adverse events were nausea (ropinirole group, 5 of 179 patients [3 percent]; levodopa group, 5 of 89 patients [6 percent]) and hallucinations (ropinirole group, 8 of 179 patients [4 percent]; levodopa group, 2 of 89 patients [2 percent]). No other individual adverse event caused the early withdrawal of 4 percent or more of the patients in either group. No more than 3 percent of the patients in either treatment group died during the study (ropinirole group, 5 of 179 patients [3 percent]; levodopa group, 2 of 89 patients [2 percent]). No deaths were directly attributed to the study medications.

DISCUSSION

This study shows that the early use of the dopamine agonist ropinirole significantly reduces the risk of dyskinesia in patients with Parkinson's disease. When all the patients randomly assigned to ropinirole were compared with those randomly assigned to levodopa, the risk of dyskinesia was lower by a factor of almost three in the ropinirole group (Fig. 2). The overall incidence of dyskinesia at five years was 20 percent in the ropinirole group, as compared with 45 percent in the levodopa group. This difference was even more striking among the patients who did not require supplementary levodopa (rates of dyskinesia: ropinirole group, 5 percent; levodopa group, 36 percent). The clinical relevance of these differences between treatment groups is emphasized by the significant difference in favor of ropinirole in the incidence of dyskinesia considered to be disabling.

These results confirm the findings of several previous open-label studies[7,9,10] and shorter blinded studies,[13,27] in which fewer motor complications were reported among patients who initially received dopamine agonists. The incidence of dyskinesia in the patients assigned to levodopa in our study differed from that reported in a five-year trial comparing immediate-release and sustained-release levodopa, in which less than 25 percent of patients had dyskinesia.[28] This difference may be related to the different doses of levodopa used and different methods of assessment of the occurrence of dyskinesia. Generally, most authors report an incidence of dyskinesia similar to that found in our study.[29]

The reason why the early use of ropinirole reduced the risk of dyskinesia remains unclear. Factors implicated as contributing to the development of dyskinesia include a higher dose of levodopa, greater severity of underlying disease,[29] and abnormal pulsatile

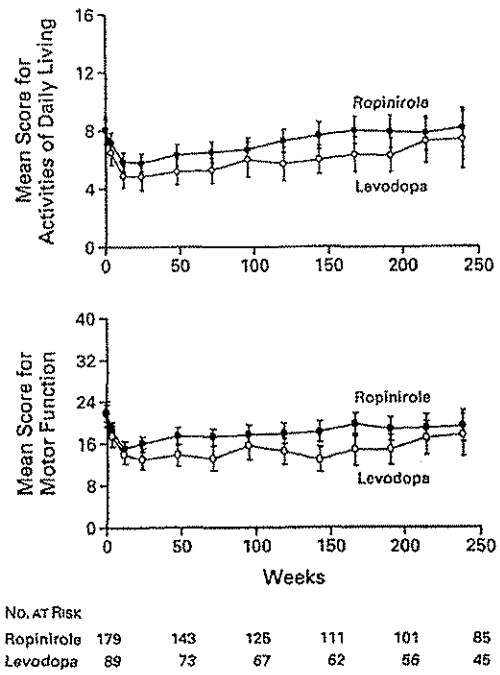


Figure 3. Mean Scores for Activities of Daily Living and Motor Function.

The scores are for part II (activities of daily living) and part III (motor function) of the Unified Parkinson's Disease Rating Scale. The range of possible scores for part II is 0 to 52; the range for part III is 0 to 108. Higher scores indicate more severe disability and more severe dysfunction. I bars indicate ±2 SE.

TABLE 2. REPORTS OF ADVERSE EVENTS OCCURRING IN 10 PERCENT OR MORE OF EITHER GROUP IN THE INTENTION-TO-TREAT ANALYSIS.

ADVERSE EVENT*	ROPINIROLE (N=179)	LEVODOPA (N=89)
	no. (%)	
Nausea	87 (48.6)	44 (49.4)
Somnolence	49 (27.4)	17 (19.1)
Insomnia	45 (25.1)	21 (23.6)
Aggravated Parkinson's disease	40 (22.3)	18 (20.2)
Dyspepsia	37 (20.7)	15 (16.9)
Dizziness	36 (20.1)	17 (19.1)
Hallucinations	31 (17.3)	5 (5.6)
Vomiting	29 (16.2)	10 (11.2)
Tremor	29 (16.2)	11 (12.4)
Abdominal pain	27 (15.1)	13 (14.6)
Depression	26 (14.5)	20 (22.5)
Headache	25 (14.0)	16 (18.0)
Edema of the legs	25 (14.0)	5 (5.6)
Ataxia	25 (14.0)	8 (9.0)
Anxiety	21 (11.7)	8 (9.0)
Postural hypotension	21 (11.7)	11 (12.4)
Constipation	17 (9.5)	11 (12.4)
Dyskinesia†	16 (8.9)	23 (25.8)
Dystonia	12 (6.7)	11 (12.4)
Increased sweating	11 (6.1)	9 (10.1)

*Patients often had more than one adverse event.

†Dyskinesia, the primary outcome measure, was assessed on the basis of both the Unified Parkinson's Disease Rating Scale and reports of adverse events.

stimulation of dopamine receptors as a result of the short elimination half-life of levodopa.[30] Ropinirole has a longer elimination half-life than levodopa (6 to 8 hours vs. 1.5 to 2 hours), thus providing more continuous stimulation of dopamine receptors. Patients treated with ropinirole also had reduced cumulative exposure to levodopa, since levodopa was used only later and at a lower dose, if necessary. The design of this study did not permit us to determine whether there was an additional neuroprotective effect of ropinirole.

The early use of ropinirole did not reduce the occurrence of wearing-off and freezing during walking to the same extent as it did the occurrence of dyskinesia. This finding suggests that these complications of motor function may not have the same pathophysiologic mechanisms as dyskinesia.

Delaying treatment with levodopa to prevent dyskinesia can be justified only if the underlying symptoms of Parkinson's disease are sufficiently controlled. The mean scores for activities of daily living remained similar in the two groups at each time point during the study (a difference of less than 1.5 points), and the changes between base line and completion of the study in the two groups were not significantly different. For the UPDRS motor score, although there was no significant difference between the two groups in the absolute value at the completion of the study, there was a significant difference in the change from base line in favor of levodopa. This difference, however, may not be clinically relevant, since it was not reflected in the measurements of activities of daily living. Moreover, the rates of early withdrawal from the study as a result of insufficient efficacy and aggravated parkinsonism were similar in the two treatment groups.

The fact that 85 of the 179 patients in the ropinirole group (47 percent) and 45 of the 89 in the levodopa group (51 percent) completed the study serves to confirm that the safety and efficacy profiles of the two treatment strategies are similar. A further measure of efficacy with respect to antiparkinson effect, sometimes used as a surrogate end point in clinical trials, is whether patients require supplementary levodopa. Although a higher percentage of ropinirole-

treated patients received supplementary levodopa than of those treated initially with levodopa in our study, this difference cannot be regarded as a reliable indicator of efficacy. The reason is that the investigators, aware of the association between levodopa and dyskinesia, appeared to be less willing to give patients with dyskinesia supplementary levodopa: of the patients in whom dyskinesia developed, only 17 percent (13 of 76) received supplementary levodopa after the onset of dyskinesia, whereas 58 percent of the patients without dyskinesia (110 of 189) received supplementary levodopa. Since dyskinesia was much more common in the levodopa group (45 percent) than in the ropinirole group (20 percent), a lower rate of supplementation in the levodopa group may have resulted.

Some physicians are cautious about using dopamine agonists, because they believe that such agents induce more adverse events (including nausea, hypotension, and hallucinations) than levodopa. This belief is based on experience gained in treating advanced Parkinson's disease, in which patients are generally older, are often receiving multiple medications, and may have a number of coexisting conditions. The doses of ropinirole administered in this study (mean, 16.5±6.6 mg per day at five years) were higher than those currently used in clinical practice in Europe and the United States. These higher doses, however, were well tolerated, with rates and profiles of adverse events that were similar for the two drugs and typical for any effective dopaminergic agent.

Neuropsychiatric adverse events are a major concern when dopamine agonists are used in the treatment of Parkinson's disease. In this study, there was no significant difference in the overall incidence of these complications, including the occurrence of somnolence, between the two treatment groups. There were no reports of falling asleep suddenly in either treatment group.[31] Although hallucinations were more frequent in the ropinirole group than in the levodopa group, they were mild and easily managed in most patients. No risk factors were identified that would predispose patients to have such adverse events with either treatment.

Our study, therefore, demonstrates that Parkinson's disease can be successfully managed for up to five years with ropinirole, with supplemental levodopa given as a second step if necessary. Such treatment significantly lowers the risk of dyskinesia as compared with treatment with levodopa alone.

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APPENDIX

The following investigators participated in the 056 Study: Belgium — P.P. De Deyn, J. Harmant, J. Jacquy; Canada — D. King, A.E. Lang, W. Martin; France — A. Destee, F. Durif, O. Rascol; Israel — J. Aharon-Peretz, A. Korczyn, A. Reches; Italy — B. Bergamasco, F. Bracco, L. Frattola, P. Nordera, G. Pezzoli, G. Scarlato, F. Stocchi; the Netherlands — A. Hovestadt; and United Kingdom — R. Abbott, M. Bakheit, G. Boddie, D.J. Brooks, C.E. Clarke, R. Corston, C. Hawkes, C. Kennard, L. Loizou, L. McLellan, D. Park, H. Sagar, E. Spokes, C. Ward, S.V. Wroe.

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Exhibit G

NEUROLOGY

Practice parameter: Initiation of treatment for Parkinson's disease: An evidence-based review: Report of the Quality Standards Subcommittee of the American Academy of Neurology

J. M. Miyasaki, W. Martin, O. Suchowersky, W. J. Weiner and A. E. Lang

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AMERICAN ACADEMY OF NEUROLOGY

Special Article

Practice parameter: Initiation of treatment for Parkinson's disease: An evidence-based review

Report of the Quality Standards Subcommittee of the American Academy of Neurology

J.M. Miyasaki, MD; W. Martin, MD; O. Suchowersky, MD; W.J. Weiner, MD; and A.E. Lang, MD

Abstract—In 1993, the last AAN Practice Parameter on medical treatment of Parkinson's disease (PD) concluded that levodopa was the most effective drug for management of this disorder. Since then, a number of new compounds including non-ergot dopamine agonists (DA) and sustained-release levodopa have been released and studied. Thus, the issue of treatment in de novo PD patients warrants reexamination. Specific questions include: 1) does selegiline offer neuroprotection; 2) what is the best agent with which to initiate symptomatic treatment in de novo PD; and 3) is there a benefit of sustained release levodopa over immediate-release levodopa? Using evidence-based principles, a literature review using MEDLINE, EMBASE, and the Cochrane Library was performed to identify all human trials in de novo PD between 1966 and 1999. Only articles that fulfilled class I or class II evidence were included. Based on this review, the authors conclude: 1) Selegiline has very mild symptomatic benefit (level A, class II evidence) with no evidence for neuroprotective benefit (level U, class II evidence). 2) For PD patients requiring initiation of symptomatic therapy, either levodopa or a DA can be used (level A, class I and class II evidence). Levodopa provides superior motor benefit but is associated with a higher risk of dyskinesia. 3) No evidence was found that initiating treatment with sustained-release levodopa provides an advantage over immediate-release levodopa (level B, class II evidence).

NEUROLOGY 2002;58:11–17

Mission statement. *The Quality Standards Subcommittee of the American Academy of Neurology is charged with developing practice parameters for neurologists for diagnostic procedures, treatment modalities, and clinical disorders. The selection of topics for which practice parameters are used is based on prevalence, frequency of use, economic impact, membership involvement, controversy, urgency, external constraints, and resources required.*

Parkinson's disease (PD) is a common neurodegenerative disorder with an estimated prevalence of 100 to 200/100,000 population. As it is a progressive disorder that results in significant disability 10 to 15 years after onset, the financial and social burden of this disease is considerable,[1] particularly with our aging population. The worldwide cost of medications alone is estimated to be US $11 billion per year, with costs increasing three- to fivefold for patients with advanced disease.[2,3]

Ideally, if a drug were available, initial treatment of PD should slow disease progression. Once symptomatic benefit is required, treatment should reduce disability without inducing complications over the long term. Based on these goals, there are several controversial questions regarding initial PD treatment. These include: Does selegiline have neuroprotective benefit in the treatment of early PD? What is the best agent to initiate specific dopaminergic therapy in early PD? Finally, is there a benefit of sustained-release levodopa over immediate-release levodopa in the treatment of early PD?

The 1993 AAN Practice Parameter examined anticholinergics, amantadine, selegiline, dopamine agonists, and levodopa in the treatment of PD.[4] The conclusions were that:

1. Levodopa is usually the most effective on average of all the drugs for symptoms of PD, especially for bradykinesia or rigidity (class I, II, III) (table 1).
2. Anticholinergic agents are commonly used as ini-

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Table 1 Levels of evidence employed in 1993

Class I	Evidence provided by one or more well-designed, randomized, controlled clinical trials.
Class II	Evidence provided by one or more well-designed clinical studies such as case control, cohort studies, etc.
Class III	Evidence provided by expert opinion, nonrandomized historical controls or case reports of one or more.

tial therapy, especially in cases where tremor is predominant, but there is evidence that anticholinergic agents are better than levodopa for tremor (class II).

3. Amantadine has a modest effect on all features of the disease and has a low adverse effect profile (class II).
4. Dopamine agonists are effective for all features of the disease, but are not generally as effective as levodopa and are more expensive than levodopa (class I, II).
5. Selegiline. Class I evidence suggests a mild therapeutic and partial protective effect from selegiline, but confirmation of the neuroprotective effect is needed. Selegiline also has antidepressant activity that offers modest direct symptomatic benefit for PD (Evidence not classified in statement).

Recent publications have compared levodopa directly to dopamine agonists (pramipexole, ropinirole and cabergoline)[5-7] in treatment of de novo (previously untreated) patients with PD. These studies were a result of concern that early use of levodopa might predispose patients to develop long-term motor complications[8] such as wearing off, dyskinesia, dystonia, and on-off phenomenon. Some studies have reported incidence of these complications as high as 80% in young patients and 44% in older patients after 5 years of levodopa treatment.[9] The frequency of dyskinesias alone is reported to range between 30 and 80% after 5 to 7 years of levodopa use. Dyskinesias may become severe with pronounced interference in the performance of activities of daily living. Hence, quality of life can be negatively and significantly affected by dyskinesias. Increasing problems with motor fluctuations also leads to use of several different medications in combination, typically at higher doses.[8,10,11]

Ideally, patients should not have to choose between accepting the inevitability of dyskinesias or unacceptable levels of disability. The goal of treatment should be to obtain an optimal reduction of parkinsonism with a minimal risk of long-term side effects. In an effort to decrease the risk of motor complications, attention has turned to initial use of dopamine agonists as monotherapy. Historically, dopamine agonist monotherapy has been thought to be poorly tolerated with decreased efficacy and a delay in onset of symptomatic benefit in comparison with levodopa.[12-15] This may not be the case with newer agonists. In addition, one of the theoretical benefits of dopamine agonists over levodopa is a longer half-life resulting in less pulsatile stimulation of dopamine receptors. This may reduce the risk of the development of dyskinesias and motor fluctuations.[16,17]

The common occurrence of the wearing-off phenomenon (end of dose bradykinesia) with immediate-release levodopa led to the development of sustained-release levodopa.[16,17] Whether motor complications are influenced by initial symptomatic treatment of PD with sustained-release levodopa versus immediate-release levodopa was investigated. Evidence comparing these two levodopa preparations is evaluated.

Literature review. To prepare this report, experienced neurologists with special expertise in PD were appointed by the Quality Standards Subcommittee (QSS). The English literature between 1966 and 2000 was searched using MEDLINE, EMBASE, and the Cochrane Library. The key words used were: early or de novo Parkinson's disease, human trials, double-blind method. Since the effectiveness of levodopa and dopamine agonists compared with placebo in the treatment of early PD is established, we focused on studies comparing dopamine agonists with levodopa. Articles were identified using the generic term dopamine agonist or specific drug names (bromocriptine, cabergoline, pergolide, lisuride, pramipexole, ropinirole). Similarly, for controlled-release versus regular or immediate-release levodopa, comparator only studies were used. In examining the neuroprotective effects of selegiline, only studies in de novo patients were evaluated. Given the controversy generated by the report of Lees et al.[18] that mortality was increased in patients with PD taking selegiline, studies utilizing selegiline in patients already receiving symptomatic therapy were included to address the safety of selegiline in this patient population.

The results of the literature search were as follows: 38 articles for selegiline were identified, two of which addressed the issue of neuroprotection. Articles were rejected for the following reasons: 13 utilized selegiline as adjunctive treatment, 5 examined symptomatic benefit only, 5 examined nonmotoric effects of selegiline, 3 were repeat publications, 3 were interim reports, 3 were commentaries on ongoing research, and 1 was a review, not a meta-analysis. Three articles addressing safety of selegiline in PD were reviewed. Seventy-eight articles for dopamine agonists used as monotherapy in de novo patients were identified; only three were long-term studies (2 years or longer) fulfilling AAN criteria for level I or II evidence (criteria defined in table 2). Articles were rejected for the following reasons: 36 utilized the dopamine agonist as adjunctive treatment, 19 did not use a levodopa (active) control, 5 utilized nonmotor endpoints, 5 provided level IV evidence, 4 were open-label studies, 3 were interim reports with subsequent publication of the complete study, 2 were repeat publications, 1 was a review article, not a meta-analysis, and 1 was a report of human toxicity. Only one article was found that examined immediate-

Table 2 Current levels of evidence classification

Rating of recommendation	Translation of evidence to recommendations	Rating of therapeutic article
A = Established as effective, ineffective or harmful for the given condition in the specified population	Level A rating requires at least one convincing class I study or at least two consistent, convincing class II studies	Class I: Prospective, randomized, controlled clinical trial with masked outcome assessment, in a representative population. The following are required: a) primary outcome(s) is/are clearly defined b) exclusion/inclusion criteria are clearly defined c) adequate accounting for dropouts and crossovers with numbers sufficiently low to have minimal potential for bias d) relevant baseline characteristics are presented and substantially equivalent among treatment groups or there is appropriate statistical adjustment for differences.
B = Probably effective, ineffective or harmful for the given condition in the specified population	Level B rating requires at least one convincing class II study or at least three consistent class III studies	Class II: Prospective matched group cohort study in a representative population with masked outcome assessment that meets a–d above OR a RCT in a representative population that lacks one criteria a through d.
C = Possibly effective, ineffective or harmful for the given condition in the specified population	Level C rating requires at least two convincing and consistent class III studies	Class III: All other controlled trials (including well-defined natural history controls or patients serving as own controls) in a representative population, where outcome assessment is independent of patient treatment.
U = Data inadequate or conflicting; given current knowledge, treatment is unproven		Class IV: Evidence from uncontrolled studies, case series, case reports, or expert opinion.

release versus sustained-release levodopa in a trial fulfilling AAN criteria for level II evidence.

Selegiline. *What is the role of selegiline in the treatment of early PD?* A neuroprotective benefit of selegiline through decreased free radical production was proposed[19] and resulted in the DATATOP (Deprenyl and Tocopherol Antioxidative Therapy of Parkinsonism) clinical trial. An interim analysis of the DATATOP trial demonstrated that selegiline reduced the risk of developing disability requiring levodopa therapy by 50%.[20] The authors concluded that this was possibly consistent with a neuroprotective effect. Further follow-up of the patient cohort revealed a symptomatic benefit of selegiline[21] with a 17.2% absolute reduction in the risk of requiring levodopa by selegiline compared with placebo. Even patients who did not experience an initial improvement in the Unified Parkinson Disease Rating Scale (UPDRS) when selegiline was started had a decreased likelihood of reaching the endpoint of requiring levodopa. These results were reported as hazard ratios and were significant. UPDRS scores had a slower rate of worsening in the selegiline group compared with placebo. In a second study examining this issue, Palhagen et al.[22] found a 4-month delay to requiring levodopa in those randomized to selegiline. The rate of decline of the motor UPDRS scores was significantly slower at 6 months. Additionally, the rate of decline of motor UPDRS scores from baseline to the end of the washout was significantly slower for the selegiline-treated patients. Since both groups[20,22] found an initial decline in functional disability during the 2-month washout period, it must be concluded that symptomatic benefit at least partially explained the reduced risk of requiring levodopa. CSF homovanillic acid levels continued to manifest changes induced by selegiline 2 months after the last administration of the drug.[23] Although these differences were not significant, it has been argued that a 2-month washout period was insufficient to completely exclude symptomatic benefit as the sole basis for the differences in selegiline versus placebo groups seen in DATATOP. In addition, if selegiline had neuroprotective effects, those taking selegiline for a longer period of time would be expected to show less evidence of clinical progression compared with those starting it later in the course of the disease. Once levodopa was initiated, motor complications would be expected to be less frequent in those who had received selegiline than in those who had not. Neither of these expectations was realized, further supporting the idea that the symptomatic effects of selegiline accounted for the delay in the need for levodopa therapy.[24,25] Both the DATATOP[20] and Palhagen et

al.[22] studies provided class II evidence that neuroprotective benefits were not seen with selegiline.

One study raised the issue of the safety of selegiline. Lees et al.[18] reported a significant excess mortality in patients receiving selegiline with levodopa (76/271) compared with those receiving levodopa alone (44/249). Concerns about this study include: the high percentage of patients withdrawn from their original treatment assignment (>50), the rerandomization of patients unable to tolerate the trial drug or gain useful functional improvement to a different arm of the trial, the inclusion of these "randomized" patients in the intention-to-treat analysis, questions about the equivalency of patient groups (specifically comorbid conditions), the predominant death certificate diagnosis of cause of death being PD in patients with relatively brief disease duration, and the difficulty reconciling the findings of this study with numerous other reports that have failed to demonstrate an increase in mortality with selegiline. A meta-analysis of prospective trials with long-term follow-up including patients with similar exposure to selegiline as in the UK Parkinson Disease Research Group study was performed.[26] There was no difference in mortality between selegiline and nonselegiline treatment groups. Analysis of levodopa plus selegiline versus levodopa alone did not reveal a difference in mortality rates. The Parkinson Study Group (PSG) reported that there was no difference in mortality in the 800 original DATATOP subjects who had been assigned to deprenyl, tocopherol, or combined treatments after an average follow-up of 8.2 years. The mortality rate observed in these patients was very similar to that expected in the age- and sex-matched US population.[27]

Conclusions. Selegiline has mild symptomatic benefit (class II). There is no convincing clinical evidence for neuroprotective benefit with selegiline (class II). There is no convincing evidence for increased mortality with selegiline whether it is given in combination with levodopa or as monotherapy (class II).

Recommendations for patients with PD who require symptomatic treatment.

- Initial symptomatic treatment of patients with PD with selegiline in order to confer mild, symptomatic benefit prior to the institution of dopaminergic therapy may be considered (level A, class II evidence).
- There is insufficient evidence to recommend the use of selegiline to confer neuroprotection in patients with PD (level U).

Initiating dopaminergic treatment. *When symptomatic therapy is required does levodopa or a dopamine agonist offer best control of motor symptoms?* Once functional disability in PD requires treatment with a dopaminergic agent, the choice of levodopa versus a dopamine agonist has been arbitrary. Decades of debate concerning this issue did not clarify the choice because the clinical trials conducted in those years were inadequate to answer the question.[28,29] In this evidenced based-review, only one article provided class I evidence comparing levodopa against pramipexole,[7] while two articles providing class II evidence compared a dopamine agonist (cabergoline 1, ropinirole 1)[5,6] versus levodopa as early monotherapy. All three of these studies compared the effect of a single agonist versus levodopa in the treatment of PD patients who were not receiving dopamine agonist or levodopa therapy. Each study was designed to allow the addition of open-label levodopa to "rescue" patients who were not doing well motorically. Although each study was designed to evaluate long-term motor complications associated with dopaminergic therapy, they also evaluated basic parameters of PD including motor response and effect on activities of daily living (ADL). The definition of motor complications and the assessment of those complications differed in each study. All dopamine agonists and levodopa demonstrated efficacy in the relief of motor symptoms.

The study of cabergoline versus levodopa by Rinne et al.[5] found that the motor portion of the UPDRS (part III) decreased by 40 to 50% with both drugs during the first year of therapy. Levodopa appeared to be better than cabergoline for improvement in both part II (ADL) and part III (motor) of the UPDRS,[30] but the publication does not report a statistical comparison of these data. After 4 years in the clinical trial, levodopa subjects still showed an average of 30% improvement in motor disability (part III), while patients treated with cabergoline showed a 22 to 23% improvement.[5] The same pattern was seen after 1 year and 4 years of treatment with regard to improvement in ADLs, again without reports of statistical comparison.

The study of ropinirole versus levodopa by Rascol et al.[6] found that for patients who completed the study (5 years), levodopa treatment resulted in a significantly greater increase in motor improvement than did ropinirole treatment (part III UPDRS, levodopa 4.8 point improvement, ropinirole 0.8 point improvement, $p = 0.008$). They also reported that there was no significant difference between the treatment groups at 5 years with regard to score on the ADL portion of the UPDRS (part II, UPDRS, + 1.6 points for ropinirole, 0.0 point change for LD, $p = 0.08$). These results suggest that for the course of the study, levodopa produced more motor improvement than ropinirole.

The study of pramipexole versus levodopa by the PSG[7] was assessed as providing class I evidence due to its lower dropout rate (13.9% compared with 48.9% withdrawal rate in the ropinirole study and insufficient reporting of withdrawals and losses to follow-up in the cabergoline study). The pramipexole study found that after 23.5 months of treatment, levodopa resulted in a significantly greater improvement than pramipexole in both the motor and ADL portions of the UPDRS (motor, levodopa 7.3 points, pramipexole 3.4 points $p < 0.001$; ADL, levodopa 2.2 points, pramipexole 1.1 points, $p = 0.001$). It should

Table 3 Levodopa versus dopamine agonists as monotherapy

Study	Parkinson Study Group[7]		Rinne et al.[5]		Rascol et al.[6]	
Level of evidence	Class I		Class II		Class II	
Agonist	Pramipexole		Cabergoline		Ropinirole	
No. of patients	301		412		268	
Study duration, y	2		3–5		5	
Efficacy	Motor*	ADL*	Motor†		Motor*	ADL*
LD	7.3	2.2	30		4.8	0
Agonist	3.4	1.1	22		0.8	1.6
Motor complications, %	All motor	Dyskinesias	All motor	Dyskinesias	Wearing off	Dyskinesias
LD	51	31	34	14	34	45
Agonist	28	10	22	6	23	20
Patients remaining on agonist alone, %	32		35		16	

* Change in UPDRS scores from baseline (absolute values).
† Percent improvement in UPDRS scores from baseline.

ADL = activities of daily living; UPDRS = Unified PD Rating Scale.

be noted that in both the ropinirole and pramipexole studies,[6,7] investigators were allowed to add open-label levodopa in the agonist-treated patients if there was insufficient symptomatic benefit from the agonist alone.

Conclusions. Levodopa, cabergoline, ropinirole, and pramipexole are effective in ameliorating motor and ADL disability in patients with PD who require dopaminergic therapy.

Levodopa is more effective than cabergoline, ropinirole, and pramipexole in treating the motor and ADL features of PD.

Initiating dopaminergic treatment. *When symptomatic therapy is required, does levodopa or a dopamine agonist offer the most favorable long-term complication profile?* All three studies[5-7] demonstrated that levodopa, cabergoline, ropinirole, or pramipexole have efficacy in alleviating motor symptoms of PD (table 3). All three of these studies defined motor complications differently. The cabergoline study used a checklist of symptoms suggesting motor fluctuations to determine the endpoint. The study staff documenting the checklist findings was not specified. The motor fluctuation abnormalities had to be present on two subsequent study visits to be considered present. Motor fluctuations in this study included wearing off, dyskinesias, and random freezing (which were also evaluated in the ropinirole and pramipexole studies). However, the motor complications checklist in the cabergoline study also included nocturnal akinesia, early morning akinesia, "off" period freezing, early morning dystonia, dose-related "off" period dystonia, and dose-related "on" period dystonia. These latter items were not evaluated in the ropinirole or pramipexole studies. The cabergoline study found an absolute risk reduction of 12% for the development of "motor complications" during the study comparing this agonist (with or without levodopa rescue) to levodopa.[5] The motor complication endpoint was reached in 22% of patients treated with cabergoline versus 34% treated with levodopa ($p < 0.02$). A subanalysis of the two most frequent motor complications (daily wearing off and peak dose dyskinesia) utilizing a Cox model revealed borderline significant difference between cabergoline and levodopa treatment for end of dose failures and a significant difference in favor of cabergoline for dyskinesias without or with levodopa. The median duration of treatment was 3.7 years. At the time of reporting, 35% of patients could be satisfactorily managed on cabergoline monotherapy. Patients included in this analysis were treated for at least 3 years and up to 5 years. Adverse events were higher in the cabergoline group (75.8%) versus levodopa (65.7%), with nausea being the most common in both.[30]

In the study of ropinirole versus levodopa,[6] the primary endpoint was dyskinesias rather than other types of motor complications. The absolute risk reduction for dyskinesias after 5 years of treatment was 26% for the ropinirole group (monotherapy or with the later addition of levodopa adjunctive therapy). If only disabling dyskinesias were considered, the absolute risk reduction was 14% in the ropinirole group (number needed to treat with 95% CI is 7 [4 to 16]). Seven patients would need to start on a dopamine agonist first strategy instead of a levodopa first strategy to prevent one additional patient from developing dyskinesias. In this study, dyskinesias were assessed using part IV of the UPDRS scale that is obtained by patient interview.

Adverse events were similar in the levodopa and ropinirole monotherapy groups, with the two most common reasons for dropping out of the study being nausea and hallucinations. The incidence of hallucinations was higher in the ropinirole group (31/179, 17%) than in the levodopa group (5/89, 6%), as was

the incidence of edema of the legs (ropinirole 25/179, 14%; versus levodopa 5/89, 6%) and somnolence (49/179, 27%; versus levodopa 17/89, 19%). However, dropout rates due to adverse events were no different in the two treatment groups. Retention of subjects in the 5-year study was 47.5% for the ropinirole group and 50.6% for the levodopa group. Among patients who completed the study and were originally randomized to ropinirole monotherapy, 16% were maintained on ropinirole monotherapy for 5 years (based on intention-to-treat analysis). A lower percentage of the levodopa group required the addition of adjunctive open-label levodopa (35.6% versus 51% taking ropinirole). The results demonstrate that initiation of treatment with ropinirole and the later addition of levodopa as necessary resulted in a significantly lower incidence of dyskinesia compared with levodopa alone.

The PSG study of pramipexole versus levodopa monotherapy in PD demonstrated similar findings.[7] Motor complications, defined as dyskinesias, wearing off, and on-off motor fluctuations, were significantly less common in the pramipexole group (28%) versus levodopa-treated patients (51%) at the end of 23.5 months. Motor complication also occurred less frequently in the pramipexole-treatment group in each of the four 6-month study periods. Most of the motor endpoints occurred after the addition of supplemental levodopa in both treatment groups. Thirty-two percent of the originally randomized group of pramipexole monotherapy patients were maintained on montherapy until the end of the study (48/151). This study also examined the impact of treatment on the quality of life of patients using the PD Quality of Life Scale (PDQUALIF) and the EuroQol. During the first 78 weeks of the trial, there was no difference in quality of life measures for either treatment group. At 102 weeks, a significant group difference in the PDQUALIF score in favor of the levodopa group was detected. This was also seen in the visual analog component of the EuroQol during the same time frame. Motor endpoints (wearing off, dyskinesias, or on-off fluctuations) in this study were prespecified and defined. One blinded investigator at each site made the judgment as to the occurrence of a dopaminergic complication.

Significantly more patients in the pramipexole group experienced somnolence ($p = 0.003$), hallucinations ($p = 0.03$), and both generalized ($p = 0.01$) and peripheral edema ($p = 0.002$) compared with those in the levodopa group. The group difference in somnolence and hallucinations emerged during the dose escalation phase of the trial and the edema difference emerged during the maintenance phase of the trial.

As noted in the 1993 practice parameter on this subject, treatment with dopamine agonists is more costly than the use of levodopa. This remains true.

Conclusions. Cabergoline, ropinirole, and pramipexole treatment of PD patients requiring dopaminergic therapy results in fewer motor complications (wearing off, dyskinesias, on-off motor fluctuations) than levodopa treatment after 2.5 years of follow-up.

Cabergoline, ropinirole, and pramipexole treatment of PD patients requiring dopaminergic therapy is associated with more frequent adverse events including hallucinations, somnolence, and edema than levodopa therapy.

Recommendations. In patients with PD who require the initiation of dopaminergic treatment, either levodopa or a dopamine agonist may be used. The choice depends on the relative impact of improving motor disability (better with levodopa) compared with the lessening of motor complications (better with dopamine agonists) for each individual patient with PD (level A, class I and class II evidence).

Sustained-release versus immediate release levodopa: When initiating levodopa therapy, which formulation should be used—immediate-release or sustained-release levodopa? Only one study compared sustained-release and immediate-release formulations of levodopa in a prospective, randomized, double-blind manner.[31] The 5-year study ("CR First") had an overall low rate of dyskinesias (20.6% immediate-release Sinemet (DuPont Pharmaceuticals, Wilmington, DE) versus 21.6% in the Sinemet CR group). The diagnostic criteria used to define the presence of dyskinesias and motor fluctuations included review of patient diaries and observations of investigators in the clinic recorded on a standard questionnaire. The only difference detected between the treatment groups was a greater improvement in activities of daily living scores in the Sinemet CR group (mean change for immediate release +0.2 compared to −0.8 in the Sinemet CR group, $p = 0.031$). The results of this study do not demonstrate sufficient differences to recommend controlled-release levodopa over immediate-release levodopa when initiating levodopa treatment. The study design initiated treatment with twice-daily dosing, thereby resulting in pulsatile stimulation from both formulations. Therefore, the lack of difference in the treatment groups may reflect poor study design rather than lack of superior efficacy.

Conclusions. When initiating therapy with levodopa, there is no difference in the rate of motor complications between immediate-release levodopa and sustained-release levodopa.

Recommendations. For patients with PD in whom levodopa treatment is being instituted, either an immediate-release or sustained-release preparation may be considered (level B, class II evidence).

Future research needs. Since there is a significant difference in the incidence of dyskinesias between levodopa monotherapy and dopamine agonist monotherapy, the relative impact of dyskinesias versus motor impairment on quality of life in PD needs to be determined. The relative importance of relief of motor symptoms compared with the impact on quality of life that dyskinesias produce would assist the neurologist in deciding which agent to utilize.

Although this parameter examined levodopa monotherapy compared with dopamine agonist monotherapy, the potential utility of combination therapy or the early addition of agonist before motor complications arise is not known. Large groups of patients in such trials would be required to enable valid conclusions to be drawn.

All the comparative trials of levodopa versus a dopamine agonist have examined levodopa monotherapy, agonist monotherapy, and agonist monotherapy plus rescue levodopa. No study has yet examined with as much detail levodopa monotherapy plus agonist rescue if motor complications appear. This would help determine if there is any long-term difference in motor performance and/or motor complications related to the initial choice of therapy in patients with PD.

Investigations of whether the early onset of mild dyskinesia or motor fluctuations predict a different outcome in patients with PD for greater than 5 years are needed.

Disclaimer. This statement is provided as an educational service of the American Academy of Neurology. It is based on an assessment of current scientific and clinical information. It is not intended to include all possible proper methods of care for a particular neurologic problem or all legitimate criteria for choosing to use a specific procedure. Neither is it intended to exclude any reasonable alternative methodologies. The AAN recognizes that specific patient care decisions are the prerogative of the patient and the physician caring for the patient, based on all of the circumstances involved.

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Appendix

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Practice parameter: Initiation of treatment for Parkinson's disease: An evidence-based review: Report of the Quality Standards Subcommittee of the American Academy of Neurology

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Neurology 2002;58;11-17

Exhibit H

(exhibit has been redacted in its entirety)

Exhibit I

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Exhibit J

(exhibit has been redacted in its entirety)

CERTIFICATE OF SERVICE

I, Patricia Smink Rogowski, hereby certify that on November 6, 2006 **Public Version of Declaration of Mark L. Rienzi in Support of Plaintiff GlaxoSmithKline's Opposition to Defendant's Motion In Limine No. 1 To Limit Evidence and Testimony on Commercial Success** was filed with the Court Clerk using CM/ECF which will send notification of such filing(s) to Josy W. Ingersoll.

I hereby further certify that on November 6, 2006, I have also served this document on the attorneys of record at the following addresses as indicated:

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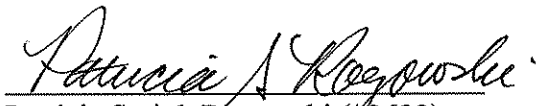

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